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Synthesis and *in vitro* antitumor activity of novel alkenyl derivatives of pyridoxine, bioisosteric analogs of feruloyl methane

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ABSTRACT

Two series of novel pyridoxine-based azaheterocyclic analogs of feruloyl methane (Dehydrozingerone, DZG) were synthesized, and their biological activity against a panel of tumor and normal cell lines was evaluated *in vitro*. The most active compounds possessed expressed cytotoxic activity, which was comparable to cytotoxic activity of doxorubicin and significantly higher than that of DZG, and a remarkable selectivity for the studied cancer cell lines as compared to the normal cells. The leading compound and DZG initiated arrest of the cell cycle in the G2/M phase, preventing normal division and further transition of daughter cells to the G0/G1 phase. Similar to DZG, but with higher efficiency, the leading compound was able to inhibit migration activity and, therefore, invasiveness of tumor cells. It also increased concentration of reactive oxygen species in tumor cells, induced depolarization of mitochondrial membranes and initiated apoptosis accompanied by disruption of integrity of cytoplasmic cell membranes. By contrast to DZG, the leading compound did not possess antioxidant properties. The obtained data make the described chemotype a promising starting point for the development of new anticancer agents.

1. Introduction

Curcumin (diferuloylmethane) (Fig. 1) is a natural product extracted from *Curcuma longa* plant with remarkable anti-oxidant, anti-inflammatory and anti-cancer activities.[1] Chemopreventive and growth inhibitory activities of curcumin against many tumor cell lines, including drug-resistant ones, have been reported.[2,3] However, the extensive preclinical and clinical studies have shown that curcumin exhibits poor bioavailability and fast metabolism,[4,5] mainly due to instability of the β-diketone fragment in neutral and basic media or in the presence of aldo-/keto-reductases *in vivo*. To address these issues, several approaches have been considered, including development of liposomal forms, nanoparticles, phospholipid complexes, and structural modifications to prepare analogs without the β-diketone moiety. In particular, asymmetric analogs of curcumin with anti-inflammatory properties were synthesized.[6] Numerous mono-carbonyl analogs of curcumin have also been obtained to improve stability and pharmacokinetic profile *in vivo*.[7,8] Such analogs have attracted attention for development of new potential anticancer, antiangiogenic and anti-inflammatory agents with enhanced bioactivity and optimized pharmacokinetic profile.

One of the most remarkable examples of mono-carbonyl analogs is feruloyl methane (Dehydrozingerone, DZG), a product of metabolic degradation of curcumin (Fig. 1). It was demonstrated that DZG is stable under physiological conditions and possesses expressed antitumor properties.[9]

It has been shown that DZG has an expressed antioxidant activity.[9,10] By analogy to curcumin, DZG inhibits formation of conjugated dienes, prevents spontaneous lipid peroxidation, and prevents Fe^{2+}/Fe^{3+} induced peroxidation.[11] DZG also reduces cisplatin-induced cytotoxicity.[9] The mechanism of antitumor action of DZG has been studied on colon cancer cells. It has been found that DZG blocks the cell cycle at G_2/M stage and increases expression of p21 protein.[9] To enhance pharmacological properties of DZG, several hybrid molecules of DZG with other natural pharmacophores have been obtained. Thus, Tatsuzaki et al. synthesized covalent conjugates of DZG with

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